

REMARKS

Claim Rejections

Claims 101, 104-106, and 111-125 are pending in the present case.

The Examiner has maintained a number of rejections. For clarity, these rejections are summarized below in the order in which they are addressed:

1. Claims 101, 104, 111-117, and 123-125 stand rejected as being allegedly being anticipated under 35 U.S.C. § 102(b) by Harrington, *et al.*, EMBO Journal vol 13:1235-1246 (1994), hereinafter "Harrington I;"
2. Claims 101, 104, 111-117, and 123-125 stand rejected as being allegedly being anticipated under 35 U.S.C. § 102(b) by Harrington, *et al.*, J. Biol. Chem 270:4503-4508 (1995), hereinafter "Harrington II;"
3. Claims 105-106 stand rejected as being allegedly being unpatentable under 35 U.S.C. § 103(a) over Harrington I in view of Dahlberg, *et al.*, patent publication WO 94/29482, hereinafter "Dahlberg;"
4. Claims 105-106 stand rejected as being allegedly being unpatentable under 35 U.S.C. § 103(a) over Harrington II in view of Dahlberg;
5. Claims 105-106, 118-119 and 122 stand rejected as being allegedly being unpatentable under 35 U.S.C. § 103(a) over Harrington I in view of Urdea;
6. Claims 105-106, 118-119 and 122 stand rejected as being allegedly being unpatentable under 35 U.S.C. § 103(a) over Harrington II in view of Urdea;
7. Claims 120-121 stand rejected as being allegedly being unpatentable under 35 U.S.C. § 103(a) over Harrington I in view of Corey;
8. Claims 120-121 stand rejected as being allegedly being unpatentable under 35 U.S.C. § 103(a) over Harrington II in view of Corey;
9. Claims 101-106 and 111-120 and 122-125 stand provisionally rejected as being unpatentable under the judicially created doctrine of obviousness-type double patenting over co-pending Application Ser. No. 11/031,487, hereinafter "'487;"

10. Claim 121 stands provisionally rejected as being unpatentable under the judicially created doctrine of obviousness-type double patenting over co-pending Application '487 in view of Corey;
11. Claims 101-106 and 111-120 and 122-125 stand provisionally rejected as being unpatentable under the judicially created doctrine of obviousness-type double patenting over co-pending Application Ser. No. 10/754,408, hereinafter "'408;"
12. Claim 121 stands provisionally rejected as being unpatentable under the judicially created doctrine of obviousness-type double patenting over co-pending Application '408 in view of Corey.

The Claims Are Not Anticipated

A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference. MPEP 2131, citing *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d. 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). As explained in more detail below, none of the references cited sets forth each and every element of the rejected claims.

1-2. Claims 101, 104, 111-117, and 123-125 stand rejected as allegedly being anticipated under 35 U.S.C. § 102(b) by Harrington, *et al.*, EMBO Journal vol 13:1235-1246 (1994), hereinafter "Harrington I. These claims also stand rejected as being allegedly being anticipated under 35 U.S.C. § 102(b) by Harrington, *et al.*, J. Biol. Chem 270:4503-4508 (1995), hereinafter "Harrington II." For reasons made of record in this application in a Response filed on September 25, 2006, and incorporated here by reference, and as further discussed below, Applicants maintain that neither Harrington I nor Harrington II teach or suggest the use of a thermostable enzyme, *i.e.*, an enzyme that is functional or active at an elevated temperature, *i.e.*, at about 55°C or higher.

The Examiner now asserts that there is reason to believe that the mammalian and yeast enzymes of Harrington I and II, enzymes that are taught in the references for use at temperatures no higher than 30°C, are active at about 55°C (Office Action, page 6). The Examiner asserts that there is homology between the mammalian and yeast enzymes of

Harrington I and II and FEN-1 nucleases isolated from thermophilic organisms, and that by reason of this homology, the thermostability of the FEN-1 enzymes for thermophilic organisms is evidence that the Harrington I and II enzymes would be active at temperatures of about 55°C (Office Action, page 6).

The Examiner's argument is not supported and is thus improper for at least the following reasons.

1. The Examiner has provided no citation to a reference indicating the degree of homology between the mammalian and yeast FEN-1 enzymes of the Harrington references and a FEN-1 enzyme from a thermophilic organism.

2. The Examiner has provided no citation to a reference that demonstrates that any such homology is sufficient to meet the requirement being "*identical or substantially identical*" to the enzymes recited in the claims, the standard required by cited passage of the MPEP for establishing anticipation.

3. The Examiner provides no reference or support for the assertion that sequence homology between the mammalian and yeast FEN-1 enzymes of the Harrington references and any FEN-1 enzymes from thermophilic organisms is predictive or in any way indicative of the temperature stabilities of the mammalian and yeast proteins.

4. The Examiner provides no reference or argument indicating why the temperature stability of a restriction enzyme is in any way predictive or indicative of the temperature stability of the mammalian and yeast FEN-1 enzymes of the Harrington references, given that these FEN-1 enzymes are not related to restriction enzymes by homology, or by the genus or species of the organism of origin.

In the absence of any specific support, the Examiner has not provided any credible reason to believe that the mammalian and yeast FEN-1 enzymes would be active or functional at any temperature above the 30°C reported by Harrington I and Harrington II. With respect to the Examiner's assertion that the term "about 55°C" is not clearly defined, Applicants submit that the specification consistently contrasts the thermostable enzymes with enzymes derived from *E. coli*, which are used at 37°C. See, e.g., the discussion of Figure 11 page 78 at lines 3-14, in which the enzymes isolated from thermophilic bacterial are used at 55°C (panel 11A), and are contrasted to enzymes from

E. coli (DNAPEcl and DNAP Klenow, the Pol I holoenzyme and Klenow fragment of Pol I of *E. coli*; page 39, lines 16 and 25), which are used at 37°C (panel 11B). As such, 37°C is clearly not within the range of "about 55°C". The 30°C temperature of operability reported for the FEN-1 enzymes of the Harrington I and II references is substantially below 37°C and thus is also clearly also not within the range of "about 55°C".

Nonetheless, for business reasons and without acquiescing to the Examiner's arguments, and reserving the right to prosecute the original or similar claims in one or more future applications, and while not altering the meaning of "thermostable" provided in the specification, Applicants herein amend Claim 101 to recite that said thermostable enzyme "functions to cleave a nucleic acid cleavage structure at a temperature of at least 55°C." This amendment is supported by numerous examples of cleavage of nucleic acid structures at reaction temperatures at or above 55°C throughout the specification. See, *e.g.*, reaction conditions described at page 100, line 13-14, page 119, lines 14-15, page 122, lines 4-5, page 132, lines 2-3.

Neither Harrington I nor Harrington II disclose the a set of reagents having the combination of 1) first and a second oligonucleotides that comprise defined regions of complementarity to a target nucleic acid such that they form an overlapped structure when annealed to the target nucleic acid, and 2) thermostable 5' nuclease that lacks synthetic activity and that functions to cleave a nucleic acid cleavage structure at a temperature of at least 55°C. As such these references do not anticipate the instant claims and Applicants respectfully request that these rejections be withdrawn.

The Claims Are Not Obvious

Prima facie obviousness requires 1) a suggestion or motivation in the references or the knowledge generally available to combine or modify the reference teachings; 2) the prior art must teach of a reasonable expectation of success should the suggested combination or modification take place; and 3) the prior art must teach or suggest all the claim limitations. MPEP § 2143. A showing of obviousness will fail if any one of these elements is not met. As explained in more detail below, none of the cited combinations of references cited sets forth each and every element of the rejected claims.

3. Claims 105-106 stand rejected as being allegedly being unpatentable under 35 U.S.C. § 103(a) over Harrington I in view of Dahlberg.

Claims 105 and 106 both depend from Claim 101 and incorporate each recited element of Claim 101. For the reasons recited above, Applicants submit that Harrington I does anticipate Claim 101 because Harrington I does not teach the recited combination of: 1) first and a second oligonucleotides that comprise defined regions of complementarity to a target nucleic acid such that they form an overlapped structure when annealed to the target nucleic acid; and 2) a thermostable 5' nuclease that lacks synthetic activity and that functions to cleave a nucleic acid cleavage structure at a temperature of at least 55°C. Dahlberg fails to overcome this deficiency. Dahlberg does not teach the recited combination of: 1) first and a second oligonucleotides that comprise defined regions of complementarity to a target nucleic acid such that they form an overlapped structure when annealed to the target nucleic acid; and 2) thermostable 5' nuclease that lacks synthetic activity and that functions to cleave a nucleic acid cleavage structure at a temperature of at least 55°C, nor does Dahlberg teach the cleavage of such overlapping structures with a thermostable 5' nuclease that lacks synthetic activity and that functions to cleave a nucleic acid cleavage structure at a temperature of at least 55°C. While Applicants do not acquiesce that the other elements necessary for establishing prima facie obviousness have been met, Applicants submit that the combination of Harrington I and Dahlberg does not teach or suggest all the limitations of Claims 105 and 106, and the cited art therefore fails to establish prima facie obviousness. Applicants respectfully request that this rejection be removed.

4. Claims 105-106 stand rejected as being allegedly being unpatentable under 35 U.S.C. § 103(a) over Harrington II in view of Dahlberg.

Claims 105 and 106 both depend from Claim 101 and incorporate each recited element of Claim 101. For the reasons recited above, Applicants submit that Harrington II does anticipate Claim 101 because Harrington II does not teach the recited combination of: 1) first and a second oligonucleotides that comprise defined regions of complementarity to a target nucleic acid such that they form an overlapped structure when annealed to the target nucleic acid; and 2) a thermostable 5' nuclease that lacks

synthetic activity and that functions to cleave a nucleic acid cleavage structure at a temperature of at least 55°C. Dahlberg fails to overcome this deficiency. Dahlberg does not teach the recited combination of: 1) first and a second oligonucleotides that comprise defined regions of complementarity to a target nucleic acid such that they form an overlapped structure when annealed to the target nucleic acid; and 2) thermostable 5' nuclease that lacks synthetic activity and that functions to cleave a nucleic acid cleavage structure at a temperature of at least 55°C, nor does Dahlberg teach the cleavage of such overlapping structures with a thermostable 5' nuclease lacking synthetic activity. While Applicants do not acquiesce that the other elements necessary for establishing prima facie obviousness have been met, Applicants submit that the combination of Harrington II and Dahlberg does not teach or suggest all the limitations of Claims 105 and 106, and the cited art therefore fails to establish prima facie obviousness. Applicants respectfully request that this rejection be removed.

5. Claims 105-106, 118-119 and 122 stand rejected as being allegedly being unpatentable under 35 U.S.C. § 103(a) over Harrington I in view of Urdea.

Claims 105-106, 118-119 and 122 depend from Claim 101 and incorporate each recited element of Claim 101. For the reasons recited above, Applicants submit that Harrington I does anticipate Claim 101 because Harrington I does not teach the recited combination of: 1) first and a second oligonucleotides that comprise defined regions of complementarity to a target nucleic acid such that they form an overlapped structure when annealed to the target nucleic acid; and 2) a thermostable 5' nuclease that lacks synthetic activity and that functions to cleave a nucleic acid cleavage structure at a temperature of at least 55°C. Urdea fails to overcome this deficiency. Urdea teaches the cleavage of a labeled oligonucleotide on a solid support using, *e.g.*, a restriction enzyme. Urdea does not teach the recited combination of: 1) first and a second oligonucleotides that comprise defined regions of complementarity to a target nucleic acid such that they form an overlapped structure when annealed to the target nucleic acid; and 2) a thermostable 5' nuclease that lacks synthetic activity and that functions to cleave a nucleic acid cleavage structure at a temperature of at least 55°C, nor does Urdea teach the cleavage of such overlapping structures with a thermostable 5' nuclease that lacks

synthetic activity and that functions to cleave a nucleic acid cleavage structure at a temperature of at least 55°C. While Applicants do not acquiesce that the other elements necessary for establishing prima facie obviousness have been met, Applicants submit that the combination of Harrington I and Urdea does not teach or suggest all the limitations of Claims 105-106, 118-119 and 122, and cited art therefore fails to establish prima facie obviousness. Applicants respectfully request that this rejection be removed.

6. Claims 105-106, 118-119 and 122 stand rejected as being allegedly being unpatentable under 35 U.S.C. § 103(a) over Harrington II in view of Urdea.

Claims 105-106, 118-119 and 122 depend from Claim 101 and incorporate each recited element of Claim 101. For the reasons recited above, Applicants submit that Harrington II does anticipate Claim 101 because Harrington II does not teach the recited combination of: 1) first and a second oligonucleotides that comprise defined regions of complementarity to a target nucleic acid such that they form an overlapped structure when annealed to the target nucleic acid; and 2) a thermostable 5' nuclease that lacks synthetic activity and that functions to cleave a nucleic acid cleavage structure at a temperature of at least 55°C. Urdea fails to overcome this deficiency. Urdea teaches the cleavage of a labeled oligonucleotide on a solid support using, *e.g.*, a restriction enzyme. Urdea does not teach the recited combination of: 1) first and a second oligonucleotides that comprise defined regions of complementarity to a target nucleic acid such that they form an overlapped structure when annealed to the target nucleic acid; and 2) a thermostable 5' nuclease that lacks synthetic activity and that functions to cleave a nucleic acid cleavage structure at a temperature of at least 55°C, nor does Urdea teach the cleavage of such overlapping structures with a thermostable 5' nuclease that lacks synthetic activity and that functions to cleave a nucleic acid cleavage structure at a temperature of at least 55°C. While Applicants do not acquiesce that the other elements necessary for establishing prima facie obviousness have been met, Applicants submit that the combination of Harrington II and Urdea does not teach or suggest all the limitations of Claims 105-106, 118-119 and 122, and the cited art therefore fails to establish prima facie obviousness. Applicants respectfully request that this rejection be removed.

7. Claims 120-121 stand rejected as being allegedly being unpatentable under 35 U.S.C. § 103(a) over Harrington I in view of Corey.

Claims 120 and 121 depend from Claim 101 and incorporate each recited element of Claim 101. For the reasons recited above, Applicants submit that Harrington I does anticipate Claim 101 because Harrington I does not teach the recited combination of: 1) first and a second oligonucleotides that comprise defined regions of complementarity to a target nucleic acid such that they form an overlapped structure when annealed to the target nucleic acid; and 2) a thermostable 5' nuclease that lacks synthetic activity and that functions to cleave a nucleic acid cleavage structure at a temperature of at least 55°C. Corey fails to overcome this deficiency. Corey teaches the attachment of a polypeptide to a nucleic acid to enhance hybridization. Corey does not teach the recited combination of: 1) first and a second oligonucleotides that comprise defined regions of complementarity to a target nucleic acid such that they form an overlapped structure when annealed to the target nucleic acid; and 2) a thermostable 5' nuclease that lacks synthetic activity and that functions to cleave a nucleic acid cleavage structure at a temperature of at least 55°C, nor does Corey teach the cleavage of such overlapping structures with a thermostable 5' nuclease that lacks synthetic activity and that functions to cleave a nucleic acid cleavage structure at a temperature of at least 55°C. While Applicants do not acquiesce that the other elements necessary for establishing prima facie obviousness have been met, Applicants submit that the combination of Harrington I and Corey does not teach or suggest all the limitations of Claims 120 and 121, and cited art therefore fails to establish prima facie obviousness. Applicants respectfully request that this rejection be removed.

8. Claims 120-121 stand rejected as being allegedly being unpatentable under 35 U.S.C. § 103(a) over Harrington II in view of Corey.

Claims 120 and 121 depend from Claim 101 and incorporate each recited element of Claim 101. For the reasons recited above, Applicants submit that Harrington II does anticipate Claim 101 because Harrington II does not teach the recited combination of: 1) first and a second oligonucleotides that comprise defined regions of complementarity to a target nucleic acid such that they form an overlapped structure when annealed to the

target nucleic acid; and 2) a thermostable 5' nuclease that lacks synthetic activity and that functions to cleave a nucleic acid cleavage structure at a temperature of at least 55°C. Corey fails to overcome this deficiency. Corey teaches the attachment of a polypeptide to a nucleic acid to enhance hybridization. Corey does not teach the recited combination of: 1) first and a second oligonucleotides that comprise defined regions of complementarity to a target nucleic acid such that they form an overlapped structure when annealed to the target nucleic acid; and 2) a thermostable 5' nuclease that lacks synthetic activity and that functions to cleave a nucleic acid cleavage structure at a temperature of at least 55°C, nor does Corey teach the cleavage of such overlapping structures with a thermostable 5' nuclease that lacks synthetic activity and that functions to cleave a nucleic acid cleavage structure at a temperature of at least 55°C. While Applicants do not acquiesce that the other elements necessary for establishing prima facie obviousness have been met, Applicants submit that the combination of Harrington II and Corey does not teach or suggest all the limitations of Claims 120 and 121, and cited art therefore fails to establish prima facie obviousness. Applicants respectfully request that this rejection be removed.

Obviousness-type Double Patenting Rejections.

The Examiner has made the following obviousness-type double patenting rejections:

9. Claims 101, 104-106 and 111-120 and 122-125 stand provisionally rejected as being unpatentable under the judicially created doctrine of obviousness-type double patenting over co-pending Application '487.
10. Claim 121 stands provisionally rejected as being unpatentable under the judicially created doctrine of obviousness-type double patenting over co-pending Application '487 in view of Corey.
11. Claims 101, 104-106 and 111-120 and 122-125 stand provisionally rejected as being unpatentable under the judicially created doctrine of obviousness-type double patenting over co-pending Application '408.


12. Claim 121 stands provisionally rejected as being unpatentable under the judicially created doctrine of obviousness-type double patenting over co-pending Application '408 in view of Corey.

The two applications cited by the Examiner in making the above-recited obviousness-type double patenting rejections, co-pending Application Ser. No. 10/754,408, filed 01/09/2004 and co-pending Application Ser. No. 11/031,487, filed 01/07/2005, are both substantially later filed than the instant application (which was filed 02/12/2002, and which claims priority to yet earlier filed cases). In accordance with the MPEP § 804 I.B.1 procedure regarding provisional double patenting rejections involving earlier and later filed applications, Applicants respectfully request that this double patenting rejection be held in abeyance until such time as a claim is found to be allowable, and that each of these double patenting rejections then be withdrawn from this earlier filed case.

CONCLUSION

For the reasons set forth above, it is respectfully submitted that all rejections have been addressed and should be removed, and Applicants' claims should be passed to allowance. Should the Examiner believe that a telephone interview would aid in the prosecution of this application, Applicants encourages the Examiner to call the undersigned collect at (608) 218-6900.

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